AMENDMENTS

Please cancel claims 12-13 and 22-36 and amend claim 1 as shown below (clean) and in the appendix (mark-up showing additions and deletions).

1. (Amended) A method of screening a human subject for an increased risk of developing a hereditary lymphedema, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele; and

(b) screening for an increased risk of developing hereditary lymphedema from the presence or absence of said mutation, wherein the presence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele in the nucleic acid correlates with an increased risk of developing hereditary lymphedema.

REMARKS

I. Status of Claims.

Claims 1-36 were pending at the time the Office action was issued. Claims 12-13 and 22-36 were withdrawn from consideration as being drawn to a non-elected invention, and have therefore been canceled herein without prejudice to pursue the subject matter of these claims in subsequent applications, such as divisional applications. Claims 1-11 and 14-21 are under examination and stand rejected variously under 35 U.S.C. §112, first and second paragraphs, 35 U.S.C. §102(e), and 35 U.S.C. §103. The Applicants respectfully traverse these rejections.

II. Rejection of the Claims Under 35 U.S.C. §112, First Paragraph for Lack of Written Description Should be Withdrawn.

Claims 1-11, 14, 15, 18, 20 and 21 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor(s) had possession of the claimed invention at the time the application was filed.

It is the Examiner's contention that, "The specification does not have adequate description of the genus of alleles which comprise the whole genus of VEGFR-3." (Office action at p. 3.) According to the Examiner, the general knowledge in the art concerning

alleles does not provide any indication of how to readily identify these alleles and the one allele described does not provide description of all the species of the alleles that might be encompassed in this broad claim. The Applicants respectfully disagree.

A. Original Claims Clearly Satisfy the Written Description Requirement

The standard for determining compliance with the written description requirement is "... does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what was claimed ..." *In re Gosteli*, 872 F.2d 1008, 1012, 10USPQ2d 1614, 1618 (Fed. Cir. 1989). The claims at issue in the instant rejection are essentially those that were originally filed, and originally filed claims presumptively satisfy the written description requirement by clearly demonstrating what the inventors contemplated as their invention at the time of filing. See PTO Written Description Guidelines; See also *In re Koller*, 204 USPQ 702 (CCPA 1980) (original claims constitute their own description). Thus, the written description rejection of the originally filed claims was legally improper, and was inconsistent with the policy behind the written description requirement.

B. The Specification Describes the Invention Adequately.

The specification provides a description of the invention which clearly allows persons of ordinary skill in the art to recognize that the instant inventors were in possession of what they claimed. The present invention is directed to, for example, the following method recited in claim 1:

> A method of screening a human subject for an increased risk of developing a hereditary lymphedema, comprising the steps of:
> (a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele; and
> (b) screening for an increased risk of developing hereditary lymphedema from the presence or absence of said mutation, wherein the presence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele in the nucleic acid correlates with an increased risk of developing hereditary lymphedema.

The specification provides a human VEGFR-3 coding sequence. (See, e.g., SEQ ID NO:1 and page 8, lines 22.) This reference VEGFR-3 sequence can be used to compare *any* human subject's sequence, as part of the process for looking for mutations that

alter the coding sequence. Moreover, the specification provides examples of specific mutations (*e.g.*, see table 3 at page 44) which correlate with heritable lymphedema. The specification also teaches how to determine the presence or absence of a mutation in VEGFR-3 (see, *e.g.*, page 6, line 16 through to page 8 line 2). Example 1, at pages 28 line 20 through page 29 line 27 of the specification, provides specific protocols of how to determine whether family members are afflicted with hereditary lymphedema and whether a VEGFR-3 mutation correlates with lymphedema development. Thus, the specification is replete with examples of mutations which are indicative of hereditary lymphedema as well as specific instruction as to how one of skill in the art should proceed to identify further such mutations. The written description support is discussed further in the proceeding sections, but it should be clear from the foregoing that the specification is in full compliance with the written description requirement of 35 U.S.C. §112, first paragraph.

C. The Rejection is Premised on a Misapprehension of What the Applicants Are Presently Claiming.

As the Examiner correctly pointed out, "the invention is, for the purposes of the 'written description' inquiry, *whatever is now claimed.*" (Office Action at p.4 *emphasis in original.*) Careful analysis shows that the rejection failed to consider what is actually being claimed.

1. The rejection improperly focuses on DNA/allele subject matter.

The Examiner's principle concern in the rejection is that "The specification does not have adequate description of the genus of alleles which comprise the whole genus of VEGFR-3." (Office action at p. 3.) The Examiner further alleges that, "[w]ith the exception of the [one VEGFR-3] sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required...." (Office

action at p. 4.)[1] Even if these allegations were true, they would not support a rejection of ***the present claims***, because the claims are not directed to VEGFR-3 alleles.

2. The claims presently under examination are not directed to a genus of VEGFR-3 alleles.

a. Method claims 1-11.

Rejected claims 1-11 are directed to a method of screening that involves, e.g., looking for the ***presence or absence of a mutation*** in one or more of a human subject's VEGFR-3 alleles. Such a screening method does *not* require a teaching of all human VEGFR-3 alleles that exist. It is inappropriate to judge the written description of the presently claimed *methods* based on a legal standard involving *protein or DNA product* inventions. The fundamental consideration of describing what an applicant has invented is different in the context of a method of screening, diagnostic invention involving a newly discovered target than a chemical compound invention. As stated in the new written description guidelines, "The description need only describe in detail that which is new or not conventional." (See 66 FR 1106). The Patent Office's own training materials treat examples relating to methods involving DNA manipulation differently than examples involving claims to DNA. (See, *e.g.*, Examples 10 and 18 in the Revised Training Materials.)

The following excerpts from the summary of the invention illustrate the adequate description of the methods of the invention:

> In the context of assaying, the term "mutation" includes addition, deletion, and/or substitution of one or more nucleotides in the *VEGFR-3* gene sequence. The invention is demonstrated by way of non-limiting examples set forth below that identify several mutations in *VEGFR-3*, including single nucleotide polymorphisms that introduce missense mutations into the *VEGFR-3* coding sequence (as compared to the *VEGFR-3* cDNA sequence set forth in SEQ ID NO: 1) and other polymorphisms that occur in introns and that are identifiable via sequencing, restriction fragment length polymorphism, or other techniques. Example 2 provides an assay to determine whether a

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[1] The Examiner also cited the Federal Circuit's *Fiddes* opinion as legal support for the rejection. This opinion concerned an adequate written description of a DNA invention, *i.e.*, an invention of a chemical DNA compound and not methods. Indeed, the Examiner correctly points out that the claims in *Fiddes* were directed to FGF's and were found unpatentable due to lack of written description for that broad class because the specification only provided the bovine sequence (Office Action page 4). The *Amgen* and *Fiers* cases cited by the Examiner likewise pertain to DNA inventions and are factually distinguishable.

> *VEGFR-3* mutation inhibits VEGFR-3 signaling. Additional assays to study both ligand binding and signaling activities of VEGFR-3 are disclosed, *e.g.*, in U.S. Patent No. 5,776,755 and International Patent Publication No. WO 98/33917, published 06 August 1998, both of which are incorporated herein by reference in their entirety. Evidence that a VEGFR-3 mutation inhibits VEGFR-3 signaling is evidence that the mutation may have a causative role in lymphedema phenotype. However, even mutations that have no apparent causative role may serve as useful markers for heritable lymphedema, provided that the appearance of the mutation correlates reliably with the appearance of lymphedema.

(Specification at pp. 9-10.)

From this excerpt, it is clear that the screening involves analysis of a human subject's VEGFR-3 DNA or RNA to determine if the person has a mutation relative to, for example, the reference VEGFR-3 cDNA sequence set forth in SEQ ID NO: 1. *Such screening methods do not require foreknowledge or description of all VEGFR-3 alleles (although several are taught in the application); the description in the application of how to analyze a human subject's DNA, compare it to a reference sequence, and draw the proper conclusions is all that is required.* The application describes numerous nucleic acid analysis techniques that are available for practicing the assaying step of the method. (See, e.g., p. 6, lines 16-33, outlining several established nucleic acid analysis techniques that are suitable.)

The application also describes and exemplifies how to determine if a mutation correlates with a heritable lymphedema. VEGFR-3 functional considerations are discussed (e.g., tyrosine kinase mutants that are apparently causative of lymphedema), and statistical procedures are taught for determining whether newly discovered mutations segregate with familial disease. Thus, the application describes practice of this aspect of the method both at a population and a biochemical level. Without any foreknowledge of all VEGFR-3 alleles, the present application describes completely and adequately how to practice the screening methods of the invention.

If the Examiner persists in this rejection, the Applicants request that she articulate for the record exactly why knowledge of all VEGFR-3 alleles is needed to describe a screening assay.

b. Product claims 14, 15, 18, 20, and 21

The Examiner also rejected product claims 14, 15, 18, 20, and 21, but these claims are not directed to VEGFR-3 alleles either. Rather, they are directed to

oligonucleotides (claims 14-15); kits comprising oligonucleotides (claim 18); and oligonucleotide arrays.

Claim 14 recites an oligonucleotide having a sequence that is identical or complementary to a wild type VEGFR-3 sequence except for one sequence difference. Such oligonucleotides are useful for detecting Flt4 polymorphisms, and the application teaches how to correlate such polymorphisms to heritable diseases. Since the oligonucleotide is identical to wild type VEGFR-3 except for one difference, claim 14 does not require knowledge of all human (mutant) alleles. Rather, it requires knowledge of a VEGFR-3 wild type sequence, and one is provided in SEQ ID NO: 1. A similar analysis applies to claim 20.

The description for claims 15, 18, and 21 is even more straight-forward because each of these claims explicitly recites SEQ ID NO: 1 as a reference sequence. Knowledge of the entire genus of VEGFR-3 alleles is not necessary to describe oligonucleotides that match SEQ ID NO: 1 except for one position.

If the Examiner persists in the rejection, the Applicants request that she articulate for the record exactly why knowledge of all VEGFR-3 alleles is needed to describe the oligonucleotide inventions of claims 14, 15, 18, 20, and 21.

3. The recitation "at least one allele."

In the rejection the Examiner focused specifically on the recitation "at least one VEGFR-3 allele" in claim 1, for example. The reader understands that this recitation is not an attempt to claim the genus of polynucleotides that comprise all VEGFR-3 alleles. Rather, the phrase is a recognition of the fact that every person normally has two VEGFR-3 alleles, because of the diploid nature of the human genome. The examples in the application show that a mutation in only one allele is sufficient to cause or predispose a person to hereditary lymphedema. Hence, the correlation clause of the claim explains that a mutation in at least one of the human subject's alleles can correlate with an increased risk of developing lymphedema.

In light of the above observations, Applicants submit that the claimed invention was fully described in the specification as filed in compliance with the written description requirements of 35 U.S.C. §112, first paragraph and request that the rejection be withdrawn.

III. Rejection of the Claims Under 35 U.S.C. §112, First Paragraph for Lack of Enablement Should be Withdrawn.

The Examiner rejected claims 1-11, 14, 15, 18, 20 and 21 under 35 U.S.C. §112, first paragraph, alleging that the application does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims.

The Examiner's position is that the specification is enabling for a method of screening for an increased risk of developing familial lymphedema by detecting the presence of a missense mutation in the VEGFR-3 allele but it does not reasonably provide enablement for a method of screening for an increased risk of developing any lymphatic disorder by detecting the "presence or absence" of any mutation altering the sequence or expression of at least one VEGFR-3 allele. The Applicants respectfully traverse.

A The Amendment to Claim 1 to Recite Hereditary Lymphedema Renders Moot the Rejection of the Claims 1-11

The Examiner acknowledged that the specification is "...enabling for (1) a method of screening for an increased risk of developing familial lymphederma [sic]..." (Office Action, page 5). Although the specification enables screening commensurate in scope with the original claims, the Applicants have amended claim 1 to recite a method of screening a human subject for an increased risk of developing a hereditary lymphedema. This amendment renders moot the Examiner's remonstrance relating to lack of enablement for diagnosing all lymphatic disorders. The Applicants reserve the right to pursue subject matter of the original claim in subsequent applications, such as divisional applications.

B. The Specification is Enabling for the Full Scope of Screening Claims 1-11.

In advancing the lack of enablement rejection, the Examiner posits that the specification provides only enablement for the five positions in the VEGFR-3 gene enumerated at Table 3, page 34 of the specification. The teachings of the invention are exemplified by those examples but should not be limited to those examples in view of the additional guidance in the specification.

The test for enablement of whether a particular claim is supported by the disclosure is to determine whether the disclosure, at the time of filing, contained sufficient information regarding the subject matter of the claim to enable one of skill in the art to make and use the claimed invention. A disclosure need not teach and preferably should omit what

is well known to those of skill in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). As long as the specification contains at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claimed invention, then the enablement requirement under 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA, 1970); MPEP 2164.01(b).

The mere fact that some degree of experimentation may be required is not the determinative factor in the scope of enablement, it is only when the level of experimentation becomes undue that it is fatal to the enablement of an invention. Thus, the key word is undue, not experimentation. *In re Wands* 858, F.2d 731, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988). A determination of what constitutes undue experimentation in a case requires application of a test of reasonableness giving regard to the nature of the invention and the state of the art. *Id.* The test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. *Id.*

The present invention teaches that a number of mutations in VEGFR-3 (e.g.,C3360T, G2588A, G3141T, T3150C and G3164A) are predictive of hereditary lymphedema and as such the present invention provides ***a method of screening*** family members for VEGFR-3 mutations that correlates with the hereditary lymphedema phenotype. In addition to showing that the presence of a mutation in the nucleic acid that alters the encoded amino acid sequence of VEGFR-3 or expression of at least one VEGFR-3 allele correlates with an increased risk of developing a hereditary lymphedema, on a statistical level, the inventors have provided biochemical evidence that such mutations are causative of hereditary lymphedema because they disrupt VEGFR-3-mediated signaling of the lymphatic growth factor VEGF-C, a VEGFR-3 ligand.

The sequence of wild-type VEGFR-3 is provided in the specification as SEQ ID NO:1. Moreover, notwithstanding the fact that the specification only needs to provide sufficient disclosure to enable one of skill in the art to make and use the claimed invention and does not have to teach what is well known to those of skill in the art, the instant specification nevertheless provides detailed methods for determining the presence or absence of a mutation in VEGFR-3. For example, the specification at page 6, line 16 through to page 8 line 2 provides examples of well known techniques that may be used to assay for a mutation in the VEGFR-3 sequence. Additionally, as indicated at page 5, line 30, through page 6, line 15, and page 28, line 20, through page 29, line 27, the application teaches how to

determine whether an individual exhibits the signs of hereditary lymphedema. Given these specific teachings of how to screen for mutations in VEGFR-3 and how to determine whether an individual has a hereditary lymphedema phenotype, the claims of the present invention are fully enabled by the specification.

As one aspect of the rejection, the Examiner expresses concern over the large amount of experimentation necessary to evaluate every theoretical mutation to VEGFR-3. Assuming for the sake of argument that such concern were relevant to claims attempting to claim all VEGFR-3 alleles, they are *not* relevant to the screening claims of the invention, because they simply don't occur (for the most part) in human subjects. (Most hypothetical mutations are nothing more than hypothetical.) Claims 1-11 do not concern the theoretical universe of mutations to VEGFR-3, but rather concern themselves with assaying VEGFR-3 nucleic acids of human subjects, especially subjects that have familial lymphedema and could benefit most from such genetic counseling. A human subject's VEGFR-3 sequence can be analyzed by comparison to the reference sequence in SEQ ID NO: 1 to look for mutations, and can be analyzed biochemically as taught in the application for loss-of-function. Both types of analysis are enabled by the application. To the extent a mutation raises concerns of lymphedema, the individual's family pedigree can be analyzed to evaluate whether the mutation correlates with the disease, or is a mere polymorphism. The application enables this analysis also and provides working examples.[2] The Examiner has failed to identify any true "difficult tasks" for practicing *the screening* that is the subject of claims 1-11.[3]

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[2] The present invention provides a disclosure of the wild-type sequence of VEGFR-3. It further shows how to identify mutations in VEGFR-3, and also provides guidance on how one of skill in the art may determine whether an individual exhibits hereditary lymphedema. Specifically, the specification teaches biochemical assays to confirm whether new mutations identified using the teachings of the present invention will likely be causative of hereditary lymphedema (see for example, the specification at page 36-39 and page 45-46). The specification provides at least 5 working examples of such mutations and specific guidance for how to identify additional mutations. It is well within the skill of artisans practiced in this field to identify such additional mutations and to conduct and compare the described screening methods as a matter of routine laboratory practice.

[3] Furthermore, there is no requirement that Applicants provide a list of the different additions, insertions or substitutions, deletions, inversions etc., of single and/or multiple amino acid residues and polypeptide expression and characterization to determine whether or not the properties of the polypeptide are retained. In asking for such a disclosure, the Examiner's request is tantamount to requesting additional working examples of mutations in VEGFR-3 in addition to those already disclosed in the instant specification. Such an onerous requirement is in direct opposition to the established tenant that working examples are not required for an enabling disclosure. *In re Robins*, 166 USPQ 552 (CCPA 1970); *In re*

C. The claims do not state that the absence of a mutation will confer susceptibility to lymphedema.

At page 6 the Examiner expresses concern that "It is not clear that the absence of a mutation in the VEGFR-3 allele will confer an altered protein expression which in turn will confer the susceptibility to develop a lymphatic disorder." Clarification is in order.

Claim 1 recites a correlation in the screening step that says *the presence* of a mutation correlates with an increased risk of developing the disorder. One skilled in the art understands from the application that persons with two normal VEGFR-3 alleles are *not* predicted to develop hereditary lymphedema from the screening assay. The presence of the mutation correlates with the increased risk, and the absence does not. (See specification at p. 5, lines 16-26.) The concern for the amount of experimentation needed to determine positions where the absence of a mutation will confer altered expression reflects a misreading of the claims, and should be withdrawn.

D. The claims relating to oligonucleotides are enabled by the application.

The Examiner also stated that "[t]he claims read broadly on any 6-50 nucleotides of SEQ ID NO:1 of the instant application, which is 100% identical to SEQ ID NO3 of U.S. Patent 5,776,755 encoding the FLT4, a receptor tyrosine kinase, which is 4795 nucleotides long which are claimed in the instant application to be used as probes." Applicants assume that this rejection is being applied to claims 14, 15, 18, 20 and 21, as opposed to the method claims of claims 1-11. The Examiner goes on to state that, it is not clear that one skilled in the art could, without undue experimentation, select any sequence 6 nucleotides in length having any addition deletion or substitution which is to be used as a screening assay and be assured that the probe selected correctly. Applicants traverse the rejection. The Examiner notes that oligonucleotides of 18-24 bases are often selected for specificity purposes.

While the Examiner may be correct that certain hybridization procedures are performed most easily and commonly with oligonucleotides of 18-24 bases, the fact remains that the techniques taught in the application are not limited to such techniques. The

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Borkowski, 164 USPQ 642, 645 (CCPA 1970). The first paragraph of §112 requires nothing more than objective enablement. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). Thus, an example may be a "working" or a "prophetic" example, indeed the specification need not contain an example at all if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation.

Examiner's attention is directed to the patents cited at page 12, line 20, of the application, which discuss and claim arrays containing oligonucleotides commensurate with what is now being claimed. The Applicants respectfully submit that if other Examiners have determined that oligonucleotides as small as six bases are suitable for these technologies, then the same determination should be equally applicable to the present application.

In view of the foregoing, the Applicants respectfully submit that the specification and claims are in full compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. Therefore, Applicants request that the rejections be withdrawn and the claims be reconsidered.

IV. The Rejection Under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn.

Claims 1-11 and 14-17 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Applicants respectfully traverse.

The Examiner objected to the use of the term "correlates" and alleged that it should be replaced with a more precise term reflecting the invention per se. When viewed in light of the specification, the term "correlates with" is sufficiently definite and one of skill in the art would understand its meaning. For example, the term "correlates" finds explanation at page 5, lines 16-26. Moreover, the working examples (especially Example 1) provide the requisite context for "correlates" in discussing the linkage of VEGFR-3 mutations to lymphedema. Webster's dictionary defines "correlate" as bearing "...a reciprocal or mutual relationship..." or where two sets or series of things are "...present or set forth so as to show a relation with each other...". The Applicants respectfully submit that in a field of genetic screening involving linkages and probabilities, the term "correlates" is well accepted and conveys the nature of the invention with clarity to the reader.

The Examiner objected to the use of the term "sequence or expression" stating that it is not clear whether amino acid or nucleotide sequence was intended. Applicants have amended steps (a) of claim 1 to recite "encoded amino acid sequence" as recited in step (b). This amendment, which simply includes in step (a) language that was already recited in step (b), does not narrow the claim, and renders the rejection moot.

Claims 14-17 were rejected for reciting the term "wild type" when referring to the human VEGFR-3 sequence. By the term wild type, the instant specification is merely referring to the non-mutant sequence of VEGFR-3. An exemplary sequence is provided in

SEQ ID NO: 1. (See p. 21, lines 21-23.) One dictionary definition of the term "wild type" states that this term refers to "...gene ...of the type predominating in the wild population. (Glossary of Genetics and Cytogenetics, Reiger et al., Eds., Springer-Verlag, Publ., p. 568, 1976). Applicants believe this term is sufficiently clear to one of skill in the art when read in light of the specification.

For the foregoing reasons the Applicants request that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

V. Rejection of the Claims Under 35 U.S.C. §102, Should be Withdrawn.

Claims 1, 2, 5 and 6 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Alitalo et al., (U.S. Patent 6,130,071). The Applicants respectfully traverse the rejection.

In order for a claim to be anticipated, a single item of prior art must disclose each element of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q.2d 81, 90 (Fed. Cir. 1986). Thus, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As explained herein below, the claims of the instant invention are not anticipated by the reference cited by the Examiner because the reference fails to disclose either expressly or inherently, every element set forth in the claims.

The claims of the present invention are directed to a method of screening a human subject for an increased risk of developing a hereditary lymphedema, by assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the amino acid sequence of VEGFR-3 or expression of at least one VEGFR-3 allele. Contrary to the Examiners assertion, such a method is not disclosed in U.S. Patent 6,130,071. The Examiner is factually **incorrect** in asserting that VEGF-C is VEGFR-3. VEGF-C is ***a ligand for VEGFR-3 and NOT VEGFR-3 itself.*** See *e.g.*, column 3 line 50-51 of U.S. Patent 6,130,071 which specifically states that the disclosure of that document "...provides a ligand, designated VEGF-C, ***for*** the Flt4 receptor tyrosine kinase (VEGFR-3)". Hence, the Examiner's discussion about the VEGF-C teachings in the '071 patent do not in any way support a rejection of the instant claims which relate to mutations of VEGFR-3. The mutations discussed in U.S. Patent 6,130,071 are mutations in VEGF-C and not VEGFR-3. The disclosure of U.S. Patent 6,130,071 provides no teaching or suggestion of screening for

mutations in VEGFR-3 for any purpose let alone for determining whether an individual has hereditary lymphedema. Because U.S. Patent 6,130,071 does not disclose or suggest the subject matter of claims 1, 2, 5 or 6, the rejection under §102 should be withdrawn.

VI. Rejection of the Claims Under 35 U.S.C. §103, Should be Withdrawn

The Examiner rejected Claims 1, 2, 5, 6, 14 and 18-21 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Alitalo et al., in view of Ahren and Stratagene. The Applicants respectfully traverse.

As discussed above, Alitalo *et al.*, simply does not disclose all the elements of the instant claims in that the Examiner has confused the VEGF-C ligand with its receptor VEGFR-3. The portions of U.S. Patent 6,130,071 cited by the Examiner (col. 15, lines 47-67; col. 16, lines 1-6; col. 15, lines 23 and 24 and col. 15 lines 18-20) do not provide disclosure that mutations in VEGFR-3 are indicative of hereditary lymphedema. Indeed these sections are not discussing VEGFR-3, but are discussing VEGF-C (e.g., see column 15 line 64-65). Contrary to the Examiner's assertion, VEGFR-3 is ***not*** one form of VEGF-C. The Examiner cites col. 15, lines 23 and 24 in support of this erroneous conclusion. However that section of the patent states:

> "For example, the dissociation constants determined for ***one form of mature VEGF-C*** (K_D =135 pM for VEGFR-3 and K_D =410 pM for VEGFR-2) provide an indication as to the concentration of VEGF-C necessary to achieve biological effects, because such dissociation constants represent concentrations at which half of the VEGF-C polypeptide is bound to the receptors through which VEGF-C biological effects are mediated. (***emphasis added***)

It is clear from this section of the 6,130,071 patent that the term "one form" refers to VEGF-C, and the parenthetical reference to VEGFR-3 is the dissociation constant at which that form of VEGF-C binds to its VEGFR-3 receptor.

Thus, the disclosure of U.S. Patent 6,130,071 is not directed to mutations in VEGFR-3 that correlate with hereditary lymphedema. Neither the Ahern general disclosure of kits nor the Stratagene Catalogue provide any disclosure that would overcome this lack of disclosure relating to VEGFR-3 in U.S. Patent 6,130,071. Hence, an obviousness rejection of the instant claims cannot be maintained because all the limitations of the invention are not disclosed in combination of references cited by the Examiner.

Claims 1, 2, 5, and 6 cannot be rendered obvious by the combination because the references do not teach or suggest methods for screening a human subject for an increased risk of developing a hereditary lymphedema, by assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the sequence or expression of at least one ***VEGFR-3 allele***. Similarly, the invention of claims 14 and 20-21 also cannot be rendered obvious by the combination because there is no mention of oligonucleotides comprising 6-50 nucleotides or arrays of oligonucleotides that have a sequence that is identical or exactly complementary to a portion of a wild type ***human VEGFR-3*** gene sequence or VEGFR-3 coding sequence, ***except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution*** in any of the references cited by the Examiner. The invention of claims 18-19 also is nonobvious over the combined disclosure of the cited references because none of the references either alone or in combination teach or suggest kits of oligonucleotides derived from VEGFR-3.

Moreover, there is no suggestion or motivation that one of skill in the art would or should combine the teachings of these documents, and even if one of skill in the art were to fortuitously combine the teachings of the cited references, there would not be an expectation of success of achieving the instant invention. Instead, one of skill in the art would arrive at screening methods for screening for mutations in VEGF-C, and kits, arrays and oligonucleotides for use therein. Prior to the present invention, one of skill in the art simply was not aware that it was possible to screen for hereditary lymphedema by screening for mutations in at least one VEGFR-3 allele. Absent such an awareness no amount of wishful thinking will lead to an expectation of success of achieving the instant invention.

In summary, Applicants submit that the cited references, either alone or in combination, fail to teach or suggest all the elements of independent claim 1, or 14, 18 or 20 there is no motivation or suggestion to combine the teachings of the cited references; and even if one of skill in the art were to combine the references, there would be no expectation of success of achieving the claimed invention. Because the references do not establish the alleged *prima facie* obviousness of the invention of claim 1, claims 2, 5 and 6 which ultimately depend from claim 1 also are patentable over the cited references. In view of the foregoing, Applicants respectfully request that the rejections of Claims 1, 2, 5, 6 14 and 18-21 over Alitalo et al., in view of Ahern and Stratagene under 35 U.S.C. §103(a) be withdrawn.

VII. Conclusion.

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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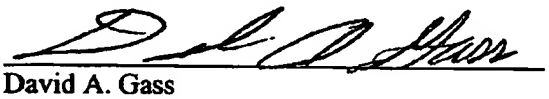
By: 

David A. Gass
Reg. No. 38,153

July 16, 2001

APPENDIX SHOWING CLAIM CHANGES

1. (Amended) A method of screening a human subject for an increased risk of developing a [lymphatic disorder] hereditary lymphedema, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele; and

(b) screening for an increased risk of developing [a lymphatic disorder] hereditary lymphedema from the presence or absence of said mutation, wherein the presence of a mutation altering the encoded amino acid sequence or expression of at least one VEGFR-3 allele in the nucleic acid correlates with an increased risk of developing [a lymphatic disorder] hereditary lymphedema.